PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
x-12553		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27801	23/11/1999	30/11/1998
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
ELI LILLY AND COMPANY et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31/05/2000	28.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stolz, B Telephone No. +49 89 2399 8416

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/27801

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-69 as originally filed

Claims, No.:

1-32 as originally filed

Drawings, sheets:

1/15-15/15 as originally filed

Sequence listing part of the description, pages:

1-4, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 4, 5, 11, 1-2 (partly), 6-10 (partly), 12-32 (partly) .

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. see above.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-10, 12-15, 24-32
	No:	Claims	1, 14, 16-23
Inventive step (IS)	Yes:	Claims	6-10, 12-15, 24-32
	No:	Claims	1-3, 14, 16-23
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Reasoned statement

1.1. The application describes a specifically pegylated non-glycosylated erythropoietin. Claimed are non-glycosylated erythropoietin (NGE), the pegylated NGE as defined in claim 6, nucleic acid sequences encoding NGE, vectors and cells, methods of making the claimed compounds and pharmaceutical uses.

1.2. Novelty (Art. 33(2) PCT)

Claim 1 relates to NGE which has been known in the art (e.g. Wasley et al.). Erythropoietin has been expressed in unglycosylated form and shown to lack in vivo activity (cf. introduction and references in WO94/25055). Therefore, claims 1, 14, 16 to 21, 23, and 32 lack novelty.

MR-NGE and NGE-166Δ have not been described in the cited prior art and are therefore novel.

1.3. Inventive step (Art. 33(3) PCT)

Claim 2 relates to NGE-166Δ. A glycosylated form of EPO lacking the C-terminal amino acid was known to exist in urine. The removal of residue 166 from NGE is therefore considered to represent an obvious modification.

The addition of MR at the N-terminus could not be derived from the cited prior art in an obvious way. However, the addition of the two amino acids does not seem to have any particular effect and is therefore considered to be an arbitrary modification. Consequently, an inventive step does not seem to be involved in arriving at the subject matter of claim 3.

As far as the claims relate to NGE pegylated as defined in claim 6 and to its uses, they seem to be inventive. Several attempts at pegylation of EPO seem to have been made (e.g. WO98/32466) and the procedure used in the present application has been tried on GM-CSF (Francis et al., 1998 (D1)). However, as can be taken from Fig. 2 of D1, pegylation of GM-CSF with PEG-aldehyde resulted in a loss of bioactivity. The remaining part of D1 deals with pegylation by TMPEG which also

results in modified EPO maintaining its activity (Figs. 4 and 7). In view of D1, the contribution to the art is the provision of an alternative EPO with improved properties. The IPEA is of the opinion that the properties of the pegylated NGE as disclosed in the application could not be derived from the cited prior art in obvious way, particularly when taking into account the teaching of D1. The subject matter of he remaining claims is therefore deemed to be inventive.

2. Certain observations

2.1. The meaning of the term NGE is open to interpretation. According to the description, it not only includes non-glycosylated EPO as obtainable by e.g. expression in a non-glycosylating host but also EPO obtained by enzymatic treatment of glycosylated EPO. This latter EPO some residues not found on the former EPO. The meaning of the term NGE must however be apparent from the wording of the claims themselves.

2.2. Claim 32 is not allowable as it does not meet the requirements of R. 6.2(a) PCT (cf. also PCT Preliminary Examination Guidelines, chapter III, 4.10).